REMARKS

Claims 70-71 have been amended as set forth in the above complete listing of the claims. Claims 62-63 are herein cancelled without prejudice or disclaimer. Thus, upon entry of the amendments, claims 64-68, and 70-72 will be pending.

Regarding the Amendments

Claims 62-63 have been cancelled without prejudice or disclaimer.

Claims 70-71 have been amended to define Applicants' invention with greater particularity. No new matter is added by the claim amendments as the amendments are fully supported by Applicants' specification and the claims as originally filed.

It is further submitted that the amendments do not require a new search or consideration, and that the amendments place the claims in condition for allowance, or in better condition for appeal. As such, it is respectfully requested that the amendments be entered.

Rejection Under 35 U.S.C. § 101

Applicants respectfully traverse the rejection of claims 62-72 under 35 U.S.C. § 101 as allegedly lacking utility.

It is stated in the Office Action that the current invention lacks a patentable utility because the specification does not disclose a credible "real world" use for the claimed nucleic acid molecules. It is further stated that the specification provides "no working examples of identification of altered levels of expression of" the claimed nucleic acids.

Applicants respectfully submit, however, that the specification clearly discloses specific and substantial utilities for the inventive nucleic acids and polypeptides, including their use as markers of seizure events in neuronal tissue. Applicants further point out that increased expression due to seizure is exemplified in three independent experimental models, each of which is a well-accepted model of seizure induction, including 1) MECS stimulation (page 68,

line 27 to page 69, line 3; page 46, Table I); 2) kainite treatment (page 69, lines 11-28; page 70, Tables II and III); and 3) pentylenetetrazole (PTZ) treatment (page 70, lines 21-27; page 71, Tables IV and V).

Applicants submit that the induction of gene expression in response to multiple experimental models of seizure and epilepsy clearly demonstrates that the up-regulated nucleic acids are indicator molecules for seizure and ischemia in neuronal tissues. Weak expression was observed in wild-type brain tissue, for example, in the pyramidal cell layers as well as the dentate gyrus of the hippocampus, thalamus, cortex, cerebellar granule cell layers, and several fiber tracts including the fimbria hippocampus and cingulum (see, for example, page 68, lines 22-27). In contrast, expression of the L100 nucleic acid (SEQ ID NO: 26) was significantly increased (17.2 fold increase) following acute seizure induced by MECS stimulation, a well-accepted model for inducing acute seizure and study of the epilepsy (page 68, line 22, to page 69, line 3).

In addition to MECS stimulation, expression of the claimed nucleic acids is strongly upregulated following acute seizures induced by kainate treatment. For example, increased expression of claimed nucleic acids (e.g., SEQ ID NO:26) upon kainite-induced seizure was confirmed by both northern analysis and in situ hybridization experiments (see, for example, page 70, Tables II and III). Furthermore, strong upregulation was observed in the dentate gyrus and areas CA3 and CA4 of the hippocampus as well as the associated entorrhinal cortex, the cingulum, and fimbria, which are brain areas known to be highly excited in and which mediate kainite-induced seizures (page 69, lines 11-28).

In yet another example provided in the specification, expression of invention nucleic acids was markedly increased in response to seizure induced by pentyleneterazole (PTZ) treatment. Consistent with the results in other models of seizure and epilepsy, expression of L100 (SEQ ID NO:26) was strongly upregulated in seizures induced by PTZ treatment, with rapidly increased expression occurring both in the hippocampus and cortex (see, for example, page 70, line 21, to page 71, line 20; and page 71, Tables IV and V). As such, these results, along with the results of upregulation in other seizure models, clearly indicate that the inventive

nucleic acids and polynucleotides are useful markers of identified, physiologically significant events: i.e., seizure events in neuronal tissues.

Applicants further submit that the asserted specific and substantial utilities of the inventive nucleic acids and polypeptides are credible because, as disclosed in the specification, the experimental models, including MECS stimulation, kainate treatment, and PTZ treatment, are each well-accepted models of seizure induction. For example, the specification provides that MECS induction is considered a model to study brain function (see, for example, page 8, lines 7-10). Additionally, Loscher et. al. (*Epilepsy Res.* 2:145-181 (1988), a copy of which is re-submitted herewith as Exhibit A) provide that MECS stimulation is a well-accepted model of acute seizure and is "probably the best validated test" for predicting drug effectiveness in treating grand mal seizures (see, for example, Loscher et. al., page 160, second column). Kainate-induced seizure is another well-known model used to study seizures and epilepsy (see, for example, page 69, lines 12-13; see also, Loscher et. al., page 148). The PTZ-induced seizure model is also well known in the art for studying epileptic seizure (see, for example, page 70, lines 22-23). Loscher et. al. indicate that PTZ induced seizures are "widely used as a standard model" for studying epilepsy (see, page 160, second column) and "widely used as a model that predicts drugs effective against generalized seizures" including petit mal seizures (see, page 154, second column). As such, it is submitted that, as disclosed in the specification and confirmed by Exhibit A, the disclosed experimental models are well-known and validated models for studying seizure and epilepsy. Therefore, absent objective evidence to the contrary, Applicants submit that there is no reason to believe that the inventive nucleic acids and polypeptides are not useful as markers of seizure events in neuronal tissue.

It is further stated in the Office Action that "no evidence has been brought forth that the polypeptide encoded by the claimed nucleic acids has a specific activity associated with seizures or ischemia." Although it is maintained that the claimed molecules have a substantial and specific utility, for example, as markers of seizure in neuronal tissues, Applicants point out that evidence is disclosed in the specification supporting L100 function to sequester zinc *in vivo*.

For example, L100 expression patterns correspond with neuronal cell populations known to release Zinc into the synapse via synaptic vesicles and to take-up Zinc post-synaptically, and L100 includes a metallothionine-like motif, which enables binding of Zinc or other divalent cations *in vivo* (page 69, lines 4-10). Further, it is known that synaptic release and uptake of Zinc may participate in the induction and maintenance of epileptic seizures and the neuronal cell death following epileptic seizures and ischemia (page 69, lines 6-8). It is therefore submitted that there is no reason to believe that the inventive molecules cannot be used as an indicator of seizure, because the increased sequestering of zinc that occurs in seizures and ischemia would be expected to be associated with increased expression of the claimed nucleic acids.

In summary, Applicants submit that the specification clearly discloses specific and substantial utilities for the claimed nucleic acids and polypeptides because induction of gene expression is exemplified in various independent experimental models and the markers are shown to be specific to seizure-related stimuli. Additionally, the evidence submitted as Exhibit A provides confirmatory evidence that the specific and substantial asserted utilities are credible. Further, in light of the role of zinc in seizure related cell damage and the disclosed functional aspects of the inventive molecules, a skilled artisan would reasonably expect seizure events to be associated with increased expression of the claimed nucleic acids. Accordingly, for the reasons set forth above, it is respectfully requested that the rejection of the claims under 35 U.S.C § 101 as allegedly lacking utility be removed.

Rejections Under 35 U.S.C. § 112

The rejection of claims 62-68 and 70-72 under U.S.C. § 112, first paragraph, as allegedly lacking enablement in conjunction with the above utility rejection, is respectfully traversed.

It is submitted that the claimed invention is adequately enabled by the specification because, as set forth above, the invention possesses a patentable utility. The specification discloses specific and substantial utilities for the claimed nucleic acids and polypeptides, for example, as specific markers of seizure events in neuronal tissue. Furthermore, the asserted

utility is exemplified in three independent experimental models, each of which is a well-accepted model of seizure induction, including 1) MECS stimulation (page 68, line 27 to page 69, line 3; page 46, Table I); 2) kainite treatment (page 69, lines 11-28; page 70, Tables II and III); and 3) pentylenetetrazole (PTZ) treatment (page 70, lines 21-27; page 71, Tables IV and V). As such, Applicants submit that one of ordinary skill in the art, viewing the specification, would be able to discern, without undue experimentation, how to use the claimed nucleic acids as specific markers of seizure in neuronal tissues. Accordingly, Applicants respectfully request the withdrawal of the rejection of claims 62-68 and 70-72 under U.S.C. § 112, first paragraph.

The rejection of claims 62-64, 66-68 and 70-71 under U.S.C. § 112, first paragraph, as allegedly lacking adequate written description, is respectfully traversed. It is initially noted that claims 62 and 63 have been cancelled, and claims 70 and 71 have been amended.

It is alleged in the Office Action that the specification does not provide disclosure adequate to convey that Applicants were in possession of the claimed nucleic acids and polypeptides. In particular, it is the Examiner's position that the specification does not adequately describe any nucleic acids or polynucleotides other than those full-length sequences that are specifically listed in the specification.

Applicants maintain that the disclosure in the specification is sufficient to apprise one skilled in the art that Applicants were in possession of the claimed nucleic acids because detailed descriptions are provided of how to identify the claimed nucleic acids structurally and functionally related to disclosed full-length nucleic acids and polypeptides. Applicants further submit that, in light of the guidance provided in the specification, identification of the claimed molecules would have been routine and within the ordinary skill of those in the art (see, MPEP § 2163 II.A.3.(a)).

The present disclosure recites a full-length nucleic acid sequence of SEQ ID NO:26, which can increase expression upon seizure induction and can influence neuronal activities involved in brain functions(page 8, lines 3-14; page 66, line 6, to page 73, line 27). From this disclosure, one of skill in the art could readily determine the structures of nucleic acids with

structures that are at least 60 percent identical or at least 85 percent identical. Similarly, a full-length amino acid sequence of SEQ ID NO:27 is disclosed, along with nucleic acids that encode amino acids with at least 60 percent identity to SEQ ID NO:27. The specification provides a detailed description of a method to determine percent identity between related sequences (see, for example, page 11, line 11 to page 12, line 16). Sequence alignment software may be used to compare positions between two sequences and, using the Jotun Heim algorithm, percent identity can be calculated. As such, those of skill in the art, viewing the specification, would recognize that Applicants were in possession of sequences with 60 or 85 percent identity to the particular full-length sequences listed in the specification (SEQ ID NO:26, SEQ ID NO:27).

It is further stated in the Office Action that claimed nucleic acids are identified only by structural characteristics and that no other distinguishing feature, such as functional or biological activity, is identified. Applicants point out, however, the claimed nucleic acids are those expressed in response to seizure or ischemia, as recited in the claims. Therefore, it is submitted that the claimed nucleic acids have both structural and functional characteristics.

It is additionally submitted that the skilled artisan would recognize that Applicants were in possession of the claimed nucleic acid sequences because the specification provides a detailed description of methods to screen such nucleic acid sequences for expression responsive to a stimulus such as seizure or ischemia. As previously asserted, invention polynucleotides and polypeptides serve as markers for specific physiologic events, such as seizure and ischemic events in neuronal tissues. The specification provides numerous protocols for assessing expression of invention nucleic acids and polypeptides in specific tissues and tissue regions. Several techniques known to those of skill in the art can be used to assess the presence of mRNA of immediate early genes including Northern blot analysis and RT-PCR (see, for example, page 66, line 6, to page 73, line 27), by in situ hybridization, and other techniques known to those of skill in the art. Thus, it would have been readily apparent at the time of filing of the invention to those of skill in the art how to determine which polynucleotides or polypeptides retain the characteristics of an immediate early gene and therefore, are encompassed by the claims.

As such, those in the art would have recognized that Applicants were in possession of the claimed molecules.

Thus, for the reasons set forth above, the specification provides adequate disclosure and guidance, such that one skilled in the art would have recognized that Applicants were in possession of the claimed nucleic acids. Accordingly, it is submitted that claims 62-64, 66-68 and 70-71 meet the written description requirement under U.S.C. § 112, first paragraph, and respectfully request removal of the rejection.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 62-68 and 70-72 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 677-1456. Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

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Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133

USPTO Customer Number 28213

Enclosure: Exhibit A